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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/534,711	03/24/2000	Philip O Livingston	53437-A-PCT-US/JPW/JL	2601

7590 08/11/2004

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EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/534,711	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,5-8 and 11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-8 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Livingston P *et al*
Priority Date: 25 September 1997

1. The examiner of the application has changed. This case has now been transferred as of 11/1/2002. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Yaen, Group Art Unit 1642.

Continued Examination Under 37 CFR 1.114

2. The request for a continued prosecution application (CPA) under 37 CFR 1.53(d) filed on 4/21/2003 is acknowledged. 37 CFR 1.53(d)(1) was amended to provide that the CPA must be for a design patent and the prior application of the CPA must be a design application that is complete as defined by 37 CFR 1.51(b). See *Elimination of Continued Prosecution Application Practice as to Utility and Plant Patent* Applications, final rule, 68 *Fed. Reg.* 32376 (May 30, 2003), 1271 *Off. Gaz. Pat. Office* 143 (June 24, 2003). Since a CPA of this application is not permitted under 37 CFR 1.53(d)(1), the improper request for a CPA is being treated as a request for continued examination of this application under 37 CFR 1.114.

3. Claims 1-2, 5-8, and 11-16 are pending and examined on the merits.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Maintained - 35 USC § 103

5. The rejection of claims 1-2, 5-8, 11, and 14-15 under 35 USC 103(a) as being obvious over Jennemann *et al* in view of Vangsted *et al* and Kensil *et al* is maintained for the reasons of record. Applicant argues that the combination of the cited references do not teach or suggest the combination of a composition comprising a fucosyl GM1 ganglioside-KLH conjugate with a QS21 carbohydrate as instantly claimed. It is noted that the examiner was in error by stating that the Jennemann *et al* taught the composition comprising GM1-KLH conjugate with a QS21 carbohydrate. However, Jennemann *et al* provides sufficient motivation for those of skill in the art to use the GM1-KLH conjugate with QS21, because the article relied upon by Jennemann *et al* (i.e. Livingston *et al* Vaccine 1994;12(14):1275-1280, IDS 1/29/2002, exhibit 13) taught the effectiveness of a composition comprising a GM2 ganglioside conjugated to KLH with a QS21 adjuvant and further indicated the ability to such an adjuvant to be effective in treating malignant melanomas. Because it was well known in the art at the time the invention was made that adjuvants such as QS21 were effective in generating high adjuvanicity and carried a low amount of toxicity, one of skill in the art would readily substitute one for the other based on these characteristics (see page 1276 of Livingston *et al*). Further as noted by the applicant on page 7 of the response filed 4/21/2003, Kensil *et al* indicates that QS21 has the ability to boost the responses to adjuvants such as KLH. Therefore given the suggestion of Jennemann *et al* in combination with Vangsted *et al* and Kinsel *et al* one of ordinary skill in the art was provided ample motivation to use QS21 in place of MPL based on adjuvanicity, low toxicity and its ability

to boost the effects of KLH and thus a composition comprising a GM1-KLH and QS21 would be reasonably expected to also elicit an enhanced ability to induce an immune response.

Applicant also argues that the examiner misinterprets the term "similar" when applied to the carbohydrates, stating that there is no indication of "similarity" between Fuc-GM1 and Glac2 ganglioside. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. Irregardless of applicant's statements, the motivation for using QS21 in place of MPL was provided by Jennemann *et al.* All other arguments concerning "similar" language is irrelevant because these are arguments of counsel of which are unsubstantiated. The term "similar" as used by Jenneman *et al* could be applied in either light and applicant has not provided sufficient objective evidence that would refute that Fuc-GM1 is not similar to Glac2. To some degree Fuc-GM1 is "similar" to Glac2 in that both are gangliosides.

Therefore the rejection of claims under 35 USC 103(a) as being obvious is maintained.

New Arguments

Claim Rejections - 35 USC § 112, 2nd paragraph

6. Claims 1-2, 5-8, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. In particular, claim 1 and its dependents recites the limitation "adjuvant" in line 7. There is insufficient antecedent basis for this limitation in the claim.

8. In particular, claim 6 and 7 recites the limitation "amount" in lines 1. There is insufficient antecedent basis for this limitation in the claim

9. In particular claims 13 and 15 fail to further limit claims 12 and 14, respectively, wherein claim 13 recites the type of cancer as being small cell lung cancer. Claims 12 and 14 are already recite the cancer as being small cell lung cancer.

Claim Rejections - 35 USC § 112, 1st paragraph

10. Claims 1-2,5-8, 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has set forth a composition comprising a Fucosyl GM1 ganglioside (herein fuc-GM1) conjugated to a keyhole limpet hemocyanin (herein KLH) and a QS-21 carbohydrate, and therefore the written description in this case is not commensurate in scope to claims that read on a composition comprising a fuc-GM1 conjugated to any immunogenic protein, and further comprising any carbohydrate derived from the Quillaja saponaria Molina tree, as claimed. Furthermore, the written description in this case has not set forth any derivative of the fuc-GM1 ganglioside nor any derivative of KLH, as claimed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The specification of the instant invention teaches the extraction and purification fuc-GM1 from thyroid glands of cows (see pages 20-21 of the specification) and the conjugation of fuc-GM1 to KLH (see page 21-22). The specification also teaches the administration of fuc-GM1-KL conjugate with QS-21 carbohydrate (see page 24-28). However, the written description in this case has not taught the broad genus of any immunogenic protein or any carbohydrate derived from the Quillaja saponaria Molina tree as claimed. Moreover, the specification has not taught "derivatives of fuc-GM1 as claimed.

There does not appear to be an adequate written description in the specification as-filed of the essential structural feature that are representative of the broad genus of "immunogenic proteins", "carbohydrates" derived from the Quillaja saponaria Molina tree, or derivatives of fuc-GM1 as claimed. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied

through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced to practice any immunogenic protein, with exception to KLH, any carbohydrate derived from the Quillaja saponaria Molina tree, with exception to QS-21, nor any derivative of fuc-GM1. Neither has Applicant provided a sufficient written description of any structure that may be correlated with the broad classes of proteins, carbohydrates or derivatives claimed. An "immunogenic protein" encompasses *any* molecule with the functional activity of eliciting an immune response, while a carbohydrate derived from the Quillaja saponaria Molina tree encompasses carbohydrates which have not been disclosed or isolated, and a derivative of fuc-GM1 encompasses any fragments, portion or part of the fuc-GM1 ganglioside. Support for immunogenic proteins is provided in the specification on page 9 lines 25-33 where it is disclosed that an immunogenic protein refers to a protein that "stimulates or enhances antibody production in the subject. Support for carbohydrates that are derived from the Quillaja saponaria Molina tree is provided in the specification on page 10, lines 10-16 where it is described as an adjuvant and encompasses "QS-21 or QS-21 like chemicals". And support for derivatives of fuc-GM1 is provided in the

specification on page 9, lines 11-20, wherein a derivative is described as an oligosaccharide portion that is derived from cleaving the ganglioside or synthesized. However, no disclosure, beyond the mere mention of immunogenic proteins, carbohydrates derived from the Quillaja saponaria Molina tree, or derivatives of the fuc-GM1 gangliosideis made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Thus the genus of compounds encompassed by these terms is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

While it is noted that some of the instant claims are drawn to methods, the claims nevertheless require an adequate written description of the composition employed in the methods.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claim Rejections - 35 USC § 112, 1st paragraph

11. Claims 12, 13, and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating small cell lung cancer comprising the administration of the composition of claim 1, does not reasonably provide enablement for a method of preventing small cell lung cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of preventing small cell lung cancer. The specification of the instant application has only provided disclosure with regard to a method of treating small cell lung cancer, but has not specifically taught one of skill in the art how to prevent small cell lung cancer comprising the administration of a composition as claimed in claim 1.

Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on

subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

Although the claims are drawn to the generation of an immune response to a carbohydrate, the underlying mechanism of action is based on the generation of an immune response to the administered antigen. Therefore, because the mechanism is similar to peptide immunotherapeutics, the teachings of Bellone *et al* and Gaiger *et al* help to highlight the unpredictable nature of cancer immunotherapy and helps to underscoere the importance of providing working examples for the prevention of cancer. Bellone *et al.* . (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Indeed, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells.

However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486). All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as in the prevention of cancer.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the pharmaceutical compositions for the prevention of small cell lung cancer as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-2,5-8, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Livingston *et al* (Vaccine 1994;12(14):1275-1280, IDS 1/29/2002, exhibit 13). Because the metes and bounds of the term "fucosyl GM1 ganglioside derivative" have not been defined in the specification as filed, for the purposes of this rejection, a "fucosyl GM1 ganglioside derivative" is interpreted to be a GM2 ganglioside. Livingston *et al* teach a composition comprising a fucosyl GM1 ganglioside derivative conjugated to a immunogenic protein, namely KLH, a QS21 carbohydrate, and a pharmaceutically

acceptable carrier (see page 1276). In particular, Livingston *et al* teaches the administration of 70μg of the ganglioside (see page 1276), and 10, 50, or 100 μg of the QS-21 carbohydrate (see page 1276). In addition, Livingston *et al* teach that the composition is effective in eliciting an antibody response in a human (see abstract).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
August 2, 2004

GARY NICKOL
PRIMARY EXAMINER